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BAL (2, 3-Dimercaptopropanol) in the Treatment of Massive Overdosage with Mapharsen

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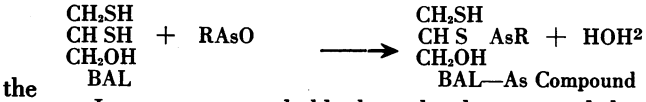
BRITISH anti-lewisite, familiarly known as BAL, was developed during the last war as an antidote for the arsenical blister gases. Although distributed to troops principally in the form of ointment to be applied in case of conjunctival or cutaneous exposure, BAL has now been shown valuable in the treatment of systemic poisoning with arsenic, gold, mercury, cadmium, and lead. Most of these applications were suggested by the extensive studies carried on in Britain and in this country. Some of the information gained in these investigations has been released in the form of large symposia, the component parts of which concern the biochemistry,[3] toxicology, pharmacology and experimental therapeutics,[18] and clinical uses[17] of BAL.*

MODE OF ACTION OF BAL

Peters, Stocken, and Thompson[21] advanced the fundamental concept that agents which combine with and inactivate the sulfhydryl groups of the activating proteins of enzyme systems, will interfere with the activity of those systems. Thus the pyruvate oxidase system[25] was found to depend upon the SH groups for its activity, and trivalent arsenicals were found to attack particularly those enzymes responsible for carbohydrate and fat metabolism.[26] At first, thiamine[13] and para-aminobenzoic acid[24] were used in an attempt to stimulate the disabled cellular economy. More promising was the finding[25] that arsenic and other heavy metals could be "detoxified" by giving compounds (particularly those with sulfhydryl groups), whose thiol groups exerted a greater affinity for arsenic than that possessed by the attacked tissue thiols. Dithiol compounds particularly were able to form a relatively stable, non-toxic, ring form thioarsenate which appeared promptly in the urine.[3a] A simple aliphatic dithiol, 2, 3-dimercaptopropanol (BAL), some of the BAL glucosides, and certain of the monothiols were the most useful of some 44 mercaptans tested in this regard.[12] The reaction is thought to be abetted by the similar spacial relationships of the SH radicals in the antidote and in the tissue proteins from which the heavy metal is displaced.[26] The reaction of arsenic with BAL may be represented as:



It seems very probable that other heavy metals besides arsenic combine with tissue proteins to interfere with tissue respiration,[14] and also that they may be attracted from the tissue proteins by BAL with which they form excretable compounds. In this group may be included antimony, bismuth (although urinary excretion does not rise), chromium, mercury, nickel,[18g] cadmium,[18f] vanadium, lead, stibium, and zinc.[29]

CHARACTERISTICS AND TOXICITY OF BAL:

2, 3-dimercaptopropanol is a colorless liquid with the typical skunk-like odor of the mercaptans. It is soluble in oil with the aid of a solubilizing agent such as 20 per cent benzyl benzoate, but it may also be prepared in an ointment base for percutaneous administration. On the skin BAL is painful, may form wheals,[17e] and cutaneous sensitization has occurred.[26]

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The opinions expressed in this paper are those of the authors, and do not necessarily reflect the official opinion of the Medical Department of the United States Army.

*BAL in a 10 per cent solution in 20 per cent peanut oil is available commercially.

Intramuscular injection of the substance in oil is less disturbing, but is often followed by intense local pain and cellulitis.[12]

Unfortunately, BAL may itself be toxic to enzyme systems. With oxygen it destroys hemin or oxyhemoglobin, reacts instantly to form hemoglobin from methemoglobin, and keeps cytochrome C in a reduced state.[29] It may inhibit brain glycolysis and the action of insulin.[29] In animals, sufficient doses may produce tremors, convulsions, coma, collapse, and death. Metabolic acidosis occurs with a lowered blood pH and CO_2 combining power, an increased serum lactic acid and amino nitrogen. Blood sugar rises initially but falls to hypoglycemic levels before death, and liver glycogen is reduced.[18a]

It has been felt that the ready penetration of BAL into the cells[30] may accentuate its toxicity to tissue metabolism. Accordingly less diffusible glucosides of BAL have been used (BAL Intrav-9) to combine with arsenic which is free in the blood stream, which diffuses out of the cells, or which may be carried from the cells to the blood by a small nontoxic dose of BAL itself.[9]

Doses of BAL less than 3 mg. per kg. of body weight produce mild reactions in about 14 per cent of cases[12] when administration occurs every four hours. Four-hourly doses of 5 mg. per kg. will cause symptoms in about 50 per cent of cases; a single dose of 8 mg. per kg. results in a marked reaction. Cumulative toxic effects which are absent with three-hourly administration of 5 mg. per kg. appear when that dose of the drug is given every two hours.[17c]

Characteristic symptoms, aside from local pain and cellulitis, are transient. They include: variable elevation of the systolic and diastolic blood pressures, most marked 45-120 minutes after injection, usually returning to normal within two hours; peripheral vasoconstriction with small doses or vascular collapse with large doses; nausea and vomiting; a burning sensation of the lips, mouth, throat, and eyes, sometimes with accompanying rhinorrhea, lacrimation, and salivation; sweating of the forehead and hands; burning and tingling of the extremities; pain in the teeth; general muscular aches; and constriction in the chest and a feeling of anxiety and agitation. The symptoms usually reach a maximum 10 to 30 minutes after injection and subside completely in the succeeding 20 to 50 minutes.[12]

Barbiturates have been suggested to diminish these effects,[26] as has epinephrine subcutaneously, or ephedrine sulphate (25 to 50 mg.) half an hour before the injection of BAL.[27]

THERAPEUTIC USES OF BAL

The dosage of BAL depends somewhat upon the metal causing the poisoning and the type and severity of the intoxication. In the treatment of acute gold toxicity (including thrombocytopenia and agranulocytosis,[19] 200 mg. of BAL given intramuscularly every four to six hours for ten doses has given good results; while 50 to 100 mg. twice daily for two to four days may relieve dermatitis.[10] It is interesting that arthritic symptoms may return following BAL-displacement of gold from its connection with the tissue sulfhydryl groups.[22] Soluble, slowly absorbed forms of gold may be more readily displaced.[10]

Mercury poisoning has been successfully treated in 25 of 26 cases by large doses of BAL: 5 mg. per kg. of body weight initially, followed by 2.5 mg. per kg. in two to four hours, and a third dose of the same size within the first 12 hours.[8,17f] Treatment of this type begun within four hours of the poisoning will save patients who ingest up to 1.5 gm. mercuric chloride.[17f]

Because of its frequency, arsenic poisoning, and particularly poisoning with the therapeutic arsenicals, has become one of the great fields of BAL usefulness. Several series of cases[1,7,11,12,15] have been reported. Eagle[11,12] from the available evidence in his large series of cases has arrived at the following schedule of BAL dosage in arsenical poisoning: in severe complications (exfoliative dermatitis, encephalitis, blood dyscrasia, jaundice, massive overdose) —3 mg. per kg. of body weight every four hours for the first two days; every six hours for the third day, and twice daily thereafter for ten days, or until recovery is evident; in mild complications (dermatitis, fever)—2.5 mg. per kg. body weight every six hours for the first two days, twice daily for the third day, and once or twice daily for the next ten or twelve days. Somewhat larger doses may be required for patients exposed to arsenical blister gas. It seems wise to err on the side of overdosage with BAL; inadequate or delayed treatment must be avoided.

With such administration of BAL, urinary excretion of arsenic rises to a peak about two hours after each injection. In some cases it may be seen to decline gradually for 4-7 days as BAL is continued. In jaundiced patients, results of excretion studies are more equivocal.[12]

In Eagle's series,[11,12] BAL therapy was associated with complete recovery of 44 of 55 patients with toxic encephalitis due to arsenic; of 10 of 11 patients with agranulocytosis; of every patient among 44 with arsenical fever; and of none of three with aplastic anemia. In 88 cases of arsenical dermatitis (51 of these exfoliative) BAL usually stopped the progression of the dermatitis and encouraged healing. Of 14 patients with jaundice (in whom needle-borne virus hepatitis must be considered), five showed prompt, and two debatable response to BAL treatment.

Of therapeutic interest is the observation that trypanosomes and spirochetes inactivated by arsenic are resuscitated by BAL.[17a]

CASE REPORTS

We have recently observed the dramatic benefits of BAL in two patients, each of whom received, through inadvertance, the contents of a ten-dose ampule of mapharsen. The injections were given at close intervals. The mistake was immediately recognized, and we were called in consultation. BAL treatment was begun within 30 minutes, an intramuscular injection of 3 mg. BAL per kg. body weight being given as the initial dose. This dose was repeated

every four hours for the first two days, every six hours for the third day, and twice daily for eight days thereafter, and once upon the twelfth and last day of treatment.

Urinary arsenic excretion levels were determined by the molybdenum blue method[16] every two hours during the first 24 hours, and subsequently upon aliquot parts of a 24 hour specimen. (See charts.)

In view of the usual effects of arsenic upon the skin,[17b,26] blood,[5,12,15,23] kidneys,[1] liver,[4,5,12,23] heart,[13] and central nervous system,[4,5,12] the patients' daily follow-up included: a physical examination, a complete hemogram, urinalysis, serum creatinine, thymol turbidity test, cephalin cholesterol flocculation test, Van den Bergh test, and electrocardiogram. The spinal fluid was examined twice. Bromsulfalein retention and blood cholesterol levels were determined periodically in each patient. Observations were repeated when the patients were completely asymptomatic, six weeks after the overdose of mapharsen. The results of all examinations were within normal limits, with the exception of those findings noted in the following reports.

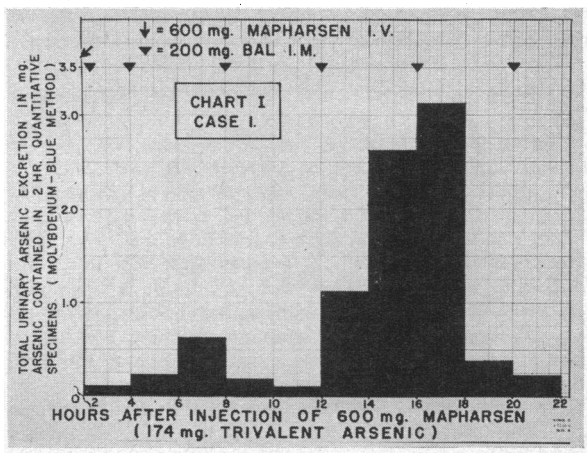

Chart 1.—Case 1: Arsenic Excretion in Urine, First day of BAL treatment.

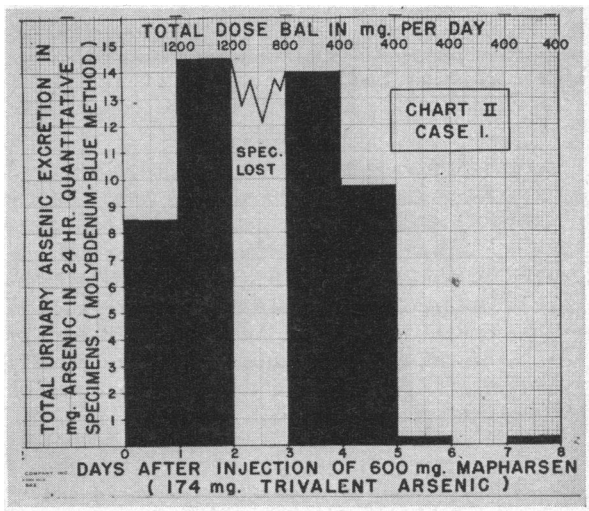

Chart 2.—Case 1: Arsenic Excretion in Urine, First week of BAL treatment.

Case 1.—The patient, a 30-year-old man, entered Letterman General Hospital on 11 July 1947 for treatment of asymptomatic neurosyphilis. A diagnosis of secondary syphilis had been made in March, 1946, and the patient was given 2,400,000 units of penicillin. At that time the spinal fluid, which contained 109 cells, was Wassermann negative. In August, 1946, the spinal fluid was Wassermann positive in all dilutions, with no pleocytosis. The patient received 10,000,000 units of penicillin intramuscularly between 31 October and 16 November 1946, and had 25 hours of therapeutic malarial fever above 104° F. between 1 November and 9 November 1946. The reactions to Wassermann and Kahn tests of the blood remained positive. On 18 July 1947 the spinal fluid Wassermann was still positive but results of Wassermann and Kahn tests of blood had become negative. It was decided to reinstitute treatment with penicillin, heavy metals, and typhoid induced pyrexia.

On 2 August 1947, the patient was inadvertently given 600 mg. of mapharsen (containing 174 mg. of trivalent arsenic). Nausea, vomiting, and some epigastric pain immediately followed the injection. BAL therapy was begun 30 minutes after the injection. The patient continued to feel nauseated, to vomit on occasion (the vomitus contained 1.2 mgm. of arsenic on analysis), and to have a loose, watery diarrhea without gross blood. He was, however, able to retain oral fluid and food, and, after the first 36 hours, became nauseated only following the injection of BAL.

Since completion of treatment, the patient has been entirely asymptomatic except for a slight scaly exfoliation of the skin of the hands and feet still noticed on 23 October 1947. Association between the BAL injection and arsenic excretion in the urine is noted in the accompanying charts 1 and 2. Serially repeated laboratory observations have revealed the following deviations from normal: Immediately following arsenic injection, the blood showed 4,000 leukocytes per cu. mm., of which 45 per cent were neutrophiles. On the second day, leukocytes had risen to 15,000 per cu. mm. with 78 per cent neutrophiles. The urine remained protein-free. Thymol turbidity test values rose to an abnormal level. A day after the injection the total Van den Bergh was 3 mgm. per 100 cc. but rapidly fell to normal limits. Six weeks following the last arsenic injection, the only abnormal laboratory finding was a persistently positive cephalin flocculation test of 3 plus. The patient has received no medication except BAL since 2 August 1947.

Case 2.—A 31-year-old Negro soldier entered Letterman General Hospital on 28 July 1947 with the diagnosis of rheumatic pericarditis. In January and again in April, 1947, at another hospital, he had had several episodes of precordial pain on exertion, and was found to have electrocardiographic changes which were interpreted as indicative of pericarditis. At the time of entry into this hospital, the patient was entirely asymptomatic and physical examination was not remarkable, except for a soft blowing, apical systolic murmur. Serial electrocardiograms and review of previous electrocardiograms were reported to show changes characteristic of sub-acute pericarditis, the cause of which was never determined. Primary syphilis was treated in 1945 with an unknown amount of penicillin, arsenic and bismuth. On entry into this hospital, results of all laboratory examinations were within normal limits, except for positive reactions to Kahn and Wassermann tests of the blood. On 9 May, 1947, the blood contained 80 Kahn units, but the Wassermann reaction was negative. At this hospital repeated Wassermann and Kahn reactions were doubtfully positive and anti-complementary, and the highest Kahn titer that could be obtained was 4 units. Cardiolipin reaction was positive. The spinal

fluid was repeatedly Wassermann negative. The syphilologist at this hospital considered this an instance of treatment failure, and advised anti-syphilis therapy to consist of 8,000,000 units of penicillin with concomitant mapharsen and bismuth.

Treatment was begun on the 25th of July, 1947. On the 2nd of August, the patient inadvertently was given 600 mgm. of marpharsen intravenously. Extreme nausea followed, and the patient complained of abdominal cramps, and vomited. (The vomitus contained 2.5 mg. arsenic on analysis.) BAL treatment was instituted 30 minutes after injection. The symptoms rapidly subsided, and except for a few loose, watery bowel movements without blood, the patient remained asymptomatic. No symptoms followed BAL injections. Urinary levels of arsenic with relation to the BAL therapy and pertinent laboratory data are shown in the accompanying charts. Serial complete blood studies, liver function tests and electrocardiograms did not reveal abnormalities. The patient remained entirely asymptomatic and six weeks following the arsenic injection, physical examination disclosed no abnormality. Results of all laboratory studies, including electrocardiograms, were also within normal limits. The Kahn titer remained 4 units. The cause of the patient's chest pain and abnormal electrocardiographic findings has not been determined.

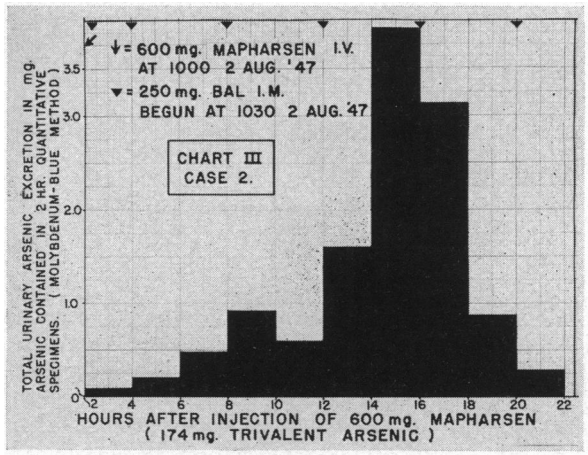

Chart 3.—Case 2: Arsenic Excretion in Urine, First day of BAL treatment.

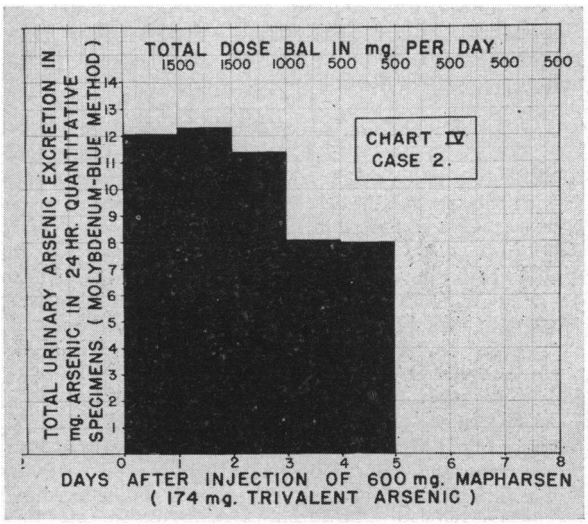

Chart 4.—Case 2: Arsenic Excretion in Urine, First week of BAL treatment.

COMMENT

In both of the cases presented the patients received a massive overdose of marpharsen and were promptly treated with BAL. Neither patient developed striking signs of BAL toxicity or the visceral toxic effects usually attributed to arsenic poisoning. The transient bilirubinemia and persistently positive reaction to the cephalin cholesterol flocculation test seen in Case 1 are of doubtful significance. The urinary excretion of arsenic during the BAL treatment of these patients is summarized in Table 1.

BAL TREATMENT OF MASSIVE OVERDOSAGE WITH MAPHARSEN

Massive overdosage with the therapeutic arsenicals is distressingly common.[4,5,6,12,23,26] Particularly frequent is the accidental administration of the contents of a ten-dose mapharsen vial (600 mg. of mapharsen or 174 mg. of arsenic). The ordinary result in such cases before the advent of BAL is well represented by Rathmell's description[23] of the case of a man who rapidly developed marked hepatomegaly, jaundice, hematemesis, hematuria, albuminuria, and nitrogen retention, and died in coma 72 hours after the arsenical injection. Postmortem examination showed multiple petechial hemorrhages, acute hepatic necrosis, kidney necrosis, and a bone marrow condition said to be indistinguishable from that found in the nutritional anemias.

Following the introduction of BAL, such maladroitness has rarely led to death. Eagle[12] discusses the treatment of four patients who received 7 to 20 times the usual dose of arsenic. The first patient received 600 mg. of mapharsen and was treated with 2.6 mg. of BAL per kg. body weight within 30 minutes. The symptoms of poisoning disappeared within 30 minutes. The patient was given 1500 mg. of BAL during the next four days. Asymptomatic jaundice appeared on the second day; the icterus index was 65 units on the fourth day, and 30 units

TABLE 1.—*Urinary Excretion of Arsenic on BAL Treatment*

	Case 1	Case 2
Trivalent Arsenic Injected	174.0 mg.	174.0 mg.
At the end of first 12 hours:		
Total BAL injected	600 mg.	750 mg.
Urinary Arsenic:		
Total excr. in mg.	8.7 mg.	12.4 mg.
Total excr. as per cent of injected Arsenic	5.0%	7.1%
At the end of second 12 hours:		
Total BAL injected	1200 mg.	1500 mg.
Urinary Arsenic:		
Total excr. in mg.	8.7 mg.	12.4 mg.
Total excr. as per cent of injected Arsenic	5.0%	7.1%
At the end of the fifth day:		
Total BAL injected	4000 mg.	5000 mg.
Urinary Arsenic:		
Total excr. in mg.	46.9 mg.	51.9 mg.
Total excr. as per cent of injected Arsenic	27.0%	30.0%

on the sixth day. The patient recovered completely. Eighty mg. of arsenic, or almost half the dose received, was excreted in the urine within the first five days. The second patient was given only 400 mg. of mapharsen and recovered with 900 mg. of BAL given over six days. The third patient developed abdominal pain and clammy perspiration following 600 mg. of mapharsen. Adequate BAL therapy was begun in 24 hours, and recovery was complete. The fourth patient received 1200 mg. of mapharsen and was given only three injections of 150 mg. BAL. He died despite an initially favorable response.

CONCLUSIONS

BAL is effective in the control of heavy metal poisoning by virtue of its ability to displace the metals from the sulfhydryl groups of the tissues where their presence interferes with cellular metabolism. It must be remembered, parenthetically, that where the metal exerts a beneficial action, as with therapeutic amounts of gold and arsenic, this action may be lost when the sulfhydryl groups are freed. Despite its own features of toxicity, BAL may now be considered the treatment of choice in poisoning with gold, mercury, or arsenic. In massive arsenical overdosage, due most often to confusion of the one-dose and ten-dose mapharsen ampules, early and adequate treatment with BAL may be expected to save life and allow complete recovery. This is demonstrated by the two cases presented. Urinary arsenic excretion studies made in these two instances indicate a striking increase in arsenic excretions during the second 12 hours of BAL therapy (when about 1,000 mgm. of BAL has been given). The total arsenic excreted in the urine amounted to about 30 per cent of the arsenic which was injected.

SUMMARY

1. BAL (2, 3-dimercaptopropanol) is briefly discussed, its value in the treatment of heavy metal poisoning with gold, mercury, or arsenic is emphasized, and dosage schedules are reviewed.

2. Two cases are presented in which BAL therapy completely counteracted the effects of a 600 mg. dose of mapharsen. Data are presented on the urinary excretion of arsenic under the influence of BAL.

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Treatment of Duodenal Ulcer by Conservative Gastric Resection with Partial Vagotomy

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THE recent introduction by Dragstedt and his associates of complete double vagotomy in the treatment of peptic ulcer has been received with considerable enthusiasm. Although this is a worthy contribution, a word of caution is probably in order. Granted that complete vagotomy has so far seemed to effect a clinical cure in most cases of duodenal ulcer, there are certain theoretical and practical objections to the use of this procedure.

Theoretically, the vagus nerves are among the most important in the body. They constitute the parasympathetic nerve supply of a large portion of the abdominal viscera, including the stomach. So far as the stomach is concerned, a variable degree of cardiospasm, pylorospasm, and gastric atony should result from the complete severance of the vagus nerve fibers. Furthermore, vagus section alone does not attack the so-called hormonal factor in the secretion of gastric acid, which is proven by the response of vagotomized patients to histamine. Some observers have stated that this factor is unimportant. This viewpoint, however, is debatable. Lahey and others have effected a cure in certain cases of stomal ulcer following gastric resection, where it was necessary at the initial operation to leave a small portion of the pyloric antrum, by subsequently reoperating upon the patient and removing this portion of the stomach.

From a practical standpoint, disturbance of motility of the stomach has seemed to be the most important objection to the procedure. Most surgeons advocating vagotomy have stated that gastric retention following vagotomy is of a transient nature. In the experience of certain others, this has not consistently been the case. McIntyre, Kipen, and the writer, on the joint graduate teaching service of the University of Southern California, the College of Medical Evangelists, and the University of California at Los Angeles, have recently started to recheck vagotomized patients who were operated on approximately a year ago at the Veterans Hospital at Sawtelle. So far, ten patients have been called back for reexamination. The studies made on these patients include roentgenograms of the stomach following a standard barium meal. This has been completed on the ten patients. In five cases in which vagotomy alone was performed the emptying time of the stomach in one was normal. In the other four there was a 24-hour retention of barium of from 30 per cent to 85 per cent. One patient with 70 per cent retention had two small gastric ulcers demonstrated by roentgenographic and gastro-

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